REMARKS

There is a correction to Table 6 presented above. We are advised that the error was a clerical error in the test data "Survival Period" of the control group. The incorrect result was "28.0" and the correct result was "29.0." The other changes resulted from recalculation.

Claims 1-14 and 29-41 are rejected under 35 USC 103(a) on the basis that Kimura et al teach analogous diphenylpyrrole compounds and that the compounds, as COX-2 inhibitors, inhibit prostaglandins. Although the rejection states that Kimura does not teach the use of these compounds to treat cachexia or disorders resulting from tumors, the rejection bridges the gap between the teaching in the Kimura and the present invention by relying on Strelkov et al to teach that the inhibition of prostaglandin production counters tumor related cachexia or muscle wasting and other deleterious side effects of tumors. From this combined teaching the rejection concludes that it would be *prima facie* obviousness to a person of ordinary skill in the art at the time the invention was made to use the diphenylpyrrole compounds of the present invention to treat cachexia or side effects of tumor related disorders. Motivation for this combination is based on the reasoning that the prior art has

established the usefulness of prostaglandin inhibitors in countering the side effects of tumors such as muscle wasting or cachexia.

Applicants respectfully submit that the reasoning set forth in the rejection is based on a hindsight selection of teaching out of context of the knowledge of persons of ordinary skill in the art with respect to this matter. When the art is taken as a whole, it is submitted that the present invention is not obvious over the teaching relied on by the Examiner as discussed in detail below.

First, Strelkov et al. does not teach that inhibition of prostaglandin production counters tumor related cachexia or muscle wasting as a certainty. There are hypotheses and possible pathways suggested, but the report is, at best, a suggestion that it might be obvious to try such procedures based on test results.

Furthermore, it is known in the art that prostaglandins are produced mainly by cyclooxygenase and that there are two types of cyclooxygenase, one is called cyclooxygenase-1 (COX-1) and the other is called cyclooxygenase-2 (COX-2) (see page 2 of Kimura et al.). Of course, a COX-2 inhibitor inhibits COX-2 and inhibits the production of prostaglandins, but it is also true that COX-1 continues to produce prostaglandins even if COX-2 is inhibited (see the enclosure annexed hereto as discussed below). Based on

these facts, applicants submit that a person of ordinary skill in the art could not know, at the time the invention was made, whether inhibiting only COX-2 was enough for cachexia to be improved. Therefore, there was no reasonable expectation for success to a person of ordinary skill that the condition of cachexia can be improved by administering a COX-2 inhibitor.

The possibility that cachexia is not expected to be treatable by a COX-2 inhibitor can be found in a later published report (1999), McCarthy (Research in Nursing & Health, 1999, 22, 380-387), a copy of which is being filed concomitant herewith in an INFORMATION DISCLOSURE STATEMENT. Although its publication date is after the filing date of he present application, it shows the results of related work. McCarthy states:

> "The findings of the present study suggest that <u>increased PG (prostaglandin) synthesis does not play a major role in the etiology of the CAC (cancer anorexia-cachexia) syndrome</u>..." (page 385, left column, lines 21-24, emphasis added).

More precisely, in the literature, ibuprofen and indomethacin, which inhibit prostaglandin production, are mentioned and it reports:

> "While the dose of each drug was sufficient to blunt the nocturnal rise in body temperature seen in placebo-treated tumor-bearing and non-tumor-bearing animals, <u>administration of ibu (ibuprofen) or indo (indomethacin) did not alter body weight or</u>

food intake of the tumor-bearing animals compared to placebo-treated tumor-bearing animals...." (page 384, right column, lines 2-8, emphasis added).

Namely, as can be understood from the statement of the literature, it could not be said that the condition of cachexia could be necessarily improved even if prostaglandin production is inhibited.

Applicants submit that this literature shows that it was not expected that the condition of cachexia can be improved by administering a COX-2 inhibitor.

Even if the art rendered it obvious to try, this is not enough. Although absolute predictability is not required for an obviousness rejection, there must be a suggestion in the art to combine references to attain the required invention, with a reasonable expectation of success. The courts have held that, "for many inventions that seem obvious, there is no absolute predictability of success until the invention is reduced to practice....To constitute obviousness under 35 USC 103 all that is required is a reasonable expectation of success." (In re O'Farrell, 7 USPQ 2d 1673, 1681, (Fed. cir. 1988).) In the present case, there was a reasonable expectation of failure based on the above.

In view of the above, withdrawal of the rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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MARKED UP VERSION OF AMENDED CLAIMS SN 09/212,556

IN THE SPECIFICATION:

Please replace Table 6 at page 53 with the following:

Table 6

Compound Name	Dose (mg/kg)	Survival Period (median: days)	Life-prolonging Index (%)
Compound 2-78	10	48.5	~~73~~ 67
Compound 2-78	3	50.5	~~80~~ 74
Compound 2-78	1	45.0	~~61~~ 55
Compound 1-94	10	45.0	~~61~~ 55
Compound 1-94	3	35.0	~~25~~ 21
Compound 1-94	1	48.5	~~43~~ 67
None	-	~~28.0~~ 29.0	0